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| 10/533,838 | 05/04/2005 | **William Brown** | 133087.03701 | 6088 |

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| EXAMINER | |
|---|---|
| ROBINSON, BINTA M | |
| **ART UNIT** | **PAPER NUMBER** |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/533,838 | BROWN ET AL. | |
| | Examiner | Art Unit | |
| | BINTA M. ROBINSON | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11 and 14-23* is/are pending in the application.

4a) Of the above claim(s) *15-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14 and 18-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## Detailed Action

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/28/08 has been entered.

2. Claim 14 is rejoined with the Group I elected invention and will be examined on the merits because it is not patentably distinct from the product compounds. Claims 12-13 are cancelled and claims 15-17 are nonelected and will not be examined.

3. The elected species is not allowable because compound 2 in claim 5 of '957 is a positional isomer of the elected species.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 14, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 8 of copending Application No. 10555980(US PG Pub 20070099957). Although the conflicting claims are not identical, they are not patentably distinct from each other because '957 discloses a genus of compounds, which are positional isomers of the instant genus of compounds.

'957 teaches the compound as shown in Formula IA, wherein R1 is hydrogen, C1-6alkyl-O-C(O), C1-6alkyl, C3-6cycloalkyl, wherein said C1-6alkyl, C3-6cycloalkyl are optionally substituted with one or more groups selected from R, NO2, OR, Br, I, F, CF3, and R is C1-6 alkyl, R4 is C1-6 alkyl or C3-6 cycloalkyl, R7 is H or C1-6 alkyl. At page 41, column 1, see the radicals defined. The difference between the prior art compound and the instantly claimed compounds is the teaching of a genus of compounds, which are positional isomers of the instant genus of compounds. The NR4(R7) moiety on the '457 compound is at the 2 position whereas in the instant compound, the analogous group which is NR2R1 is at the 3 position. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. The '457 compounds are useful in therapy and thus it would have been obvious to modify the '457 compounds to the instant compounds which are positional isomers. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for

the claimed compounds over those of the generic prior art compounds and compositions.

Claims 11 and 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 5 of copending Application No. 10555980(20070099957.) Although the conflicting claims are not identical, they are not patentably distinct from each other because '957 discloses compounds which are positional isomers of the instant compounds.

US PG Pub 20070099957 teaches the compounds in claim 5. At page 52, columns 1-2, see the '957 compounds. The difference between the prior art compound and the instantly claimed compounds is the teaching of compounds, which are positional isomers of the instant compounds. The NR4(R7) moiety on the '457 compound is at the 2 position whereas in the instant compound, the analogous group which is NR2R1 is at the 3 position. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. The '457 compounds are useful in therapy and thus it would have been obvious to modify the '457 compounds to the instant compounds which are positional isomers. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds and compositions.

Claims 1-2, 11, and 14 are directed to an invention not patentably distinct from claims 1-5 and 8 of commonly assigned application 10555980 (US PG Pub 20070099957). Specifically, this application teaches '957 teaches the instant

compound as shown in Formula IA, wherein R1 is hydrogen, C1-6alkyl-O-C(O), C1-6alkyl, C3-6cycloalkyl, wherein said C1-6alkyl, C3-6cycloalkyl are optionally substituted with one or more groups selected from R, NO2, OR, Br, I, F, CF3, and R is C1-6 alkyl, R4 is C1-6 alkyl or C3-6 cycloalkyl, R7 is H or C1-6 alkyl as well as specific compound species. At page 41, column 1, see the radicals defined and at claim 5, see the compound species. The difference between the prior art compound and the instantly claimed compounds is the teaching of a genus of compounds which are positional isomers of the instant genus of compounds and species which are positional isomers of the instant species. The NR4(R7) moiety on the '457 compound is at the 2 position whereas in the instant compound, the analogous group which is NR2R1 is at the 3 position. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. The '457 compounds are useful in therapy and thus it would have been obvious to modify the '457 compounds to the instant compounds which are positional isomers. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds and compositions over those of the generic prior art compounds and compositions.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10, 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delorme (See Reference N, WO 9828275) in view of Greene et al.Delorme teaches the compound as shown in Formula I, which is a genus of compounds which overlap in scope with the instant genus of compounds. At pages 103 –105, see the compound of formula I in claim 1. The difference between the prior art genus and the instantly claimed genus of compounds is the teaching of a generic compound which overlaps in subject matter with the instant genus of compounds. Delorme also teaches the example of compound 41, wherein the amino group at the meta position of the phenyl ring is unsubstituted, whereas, the instantly claimed invention, teaches the claimed compound, comprising an amino group at the meta position of the phenyl ring, wherein the amino group is substituted with a group such as an optionally substituted acetyl group when R1 is R8C(O), and R8 is methyl, which is optionally substituted as claimed in claim 1, page 2. Greene et. al. teaches that optionally subtituted acetyl groups are protecting groups of the amino functional group. See pages 552-558. Page 17, lines 26-28 of Delorme teach that substituents R1, R2, and R3 on the compound of formula (I) may be modified by methods known in the art , for example as exemplified in ***Protecting Groups*** by Green.

The Delorme compounds are opioid antagonists, with analgesic effects as revealed at page 1, lines 20-26 and page 2, lines 1-3, and the instant compounds are also opioid agonists that are analgesics.

It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds with the similar utilities of being opioid agonists with analgesic effects and also it would have been obvious to one of ordinary skill in the art to modify the prior art compound, such that the meta amino group is protected. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 7, 8, 10, 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 8, 15, 16, 18 of copending Application No. 10596850 (20070219249) in view of Greene et. al. Although the conflicting claims are not identical, they are not patentably distinct from

each other because the copending application teaches a genus of compounds and compositions containing them which overlaps in subject matter with the instant compounds and compositions, the difference being that the non-amido - nitrogen on the phenyl ring of the compound is protected with a nitrogen protecting group such as acetyl.

The Copending application teaches a genus of compounds and compositions containing them at example claim 1 and claim 8. The difference between the prior art compound and compositions and the instantly claimed compounds and compositions is the teaching of a genus of compounds wherein the nonamido nitrogen is protected with nitrogen protecting group such as acetyl. Greene et. al. teaches that nitrogen can be protected with various protecting groups such as optionally substituted acetyl. See pages 552-558. It would have been obvious to one of ordinary skill in the art to produce a genus of compounds which overlap in subject matter with the '850 compounds and deprotect the amino nitrogen so that amino nitrogen is an unprotected. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds and compositions over those of the generic prior art compounds and compositions.

Claims 1, 5, 8 and 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 8, 13, 19-22 of copending Application No. 10541522 (US PG Pub 20060154964) in view of Greene et. al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims a genus of compounds

which overlap in subject matter with the instant genus of compounds and whose primary difference is at the R3 moiety as reflected in the instant genus of compounds -the difference being that the amino nitrogen in the piperidine ring is protected in the copending compound whereas it can be a free amino group in the instant genus of compounds and compositions containing them.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

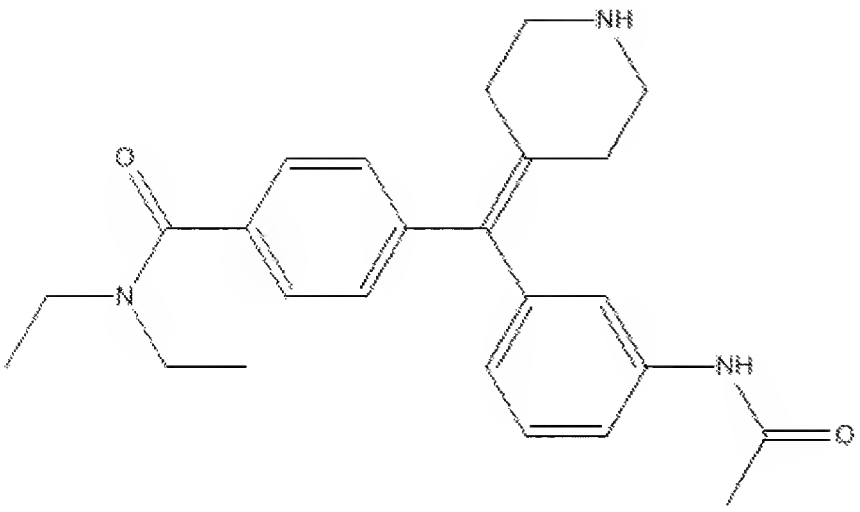
The Copending application teaches a genus of compounds and compositions containing them. The difference between the Copending compounds and compositions and the instantly claimed compounds and compositions is the teaching of a genus of compounds wherein the R3 moiety is a protecting group in the copending compound whereas it can be a hydrogen in the instant genus of compounds and compositions containing them.

Greene teaches that nitrogen can be protected with various protecting groups such as benzyl optionally substituted with groups such as methoxy or hydroxy. See pages 531-539. It would have been obvious to one of ordinary skill in the art to produce a genus of compounds which overlap in subject matter with the '522 compounds and to deprotect the amino nitrogen in the piperidinyl ring so that amino nitrogen has a free hydrogen. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds and compositions over those of the generic prior art compounds and compositions.

Claims 1, 5, 8 and 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 13 of copending Application No. 10541522 (US PG Pub 20060154964). Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches a genus of compounds and compositions containing them which overlap in subject matter with the instant genus of compounds and compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

'522 et. al. teaches the genus of compounds as shown in Formula III, where R4 is C1-6 alkyl, R5 is hydrogen, or C1-6 alkyl, optionally substituted with Br, F, I, Cl, CF3, R2 an R3 ethyl. At page 4, claim 13, see the compound of formula III. The difference between the prior art compound and the instantly claimed compounds is the teaching of a generic compound which overlaps in subject matter with the instant genus of compounds. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. For instance, see the compound,




of claim 23 , where a disclosed species is exemplified. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds and compositions over those of the generic prior art compounds and compositions.

8. Claims 1, 5, 8 and 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 8, 19-21 of copending Application No. 10541656 (US PG Pub 20060116399) in view of Greene et. al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims a genus of compounds which overlap in subject matter with the instant genus of compounds and whose primary difference is at the R3 moiety as reflected in the instant genus of compounds -the difference being that the amino nitrogen in the piperidine ring is protected in the copending compound whereas it can be a free amino group in the instant genus of compounds and compositions containing them.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The Copending application teaches a genus of compounds and compositions containing them, of formula I wherein R1 can be C6 aryl, optionally substituted with OR wherein R is methyl, or hydrogen, R2 and R3 is ethyl, R4 is C1-6 alkyl. The difference between the Copending compounds and compositions and the instantly claimed compounds and compositions is the teaching of a genus of compounds wherein the moiety equivalent to the instant R3 group is a protecting group in the copending compound whereas it can be a hydrogen in the instant genus of compounds and compositions containing them.

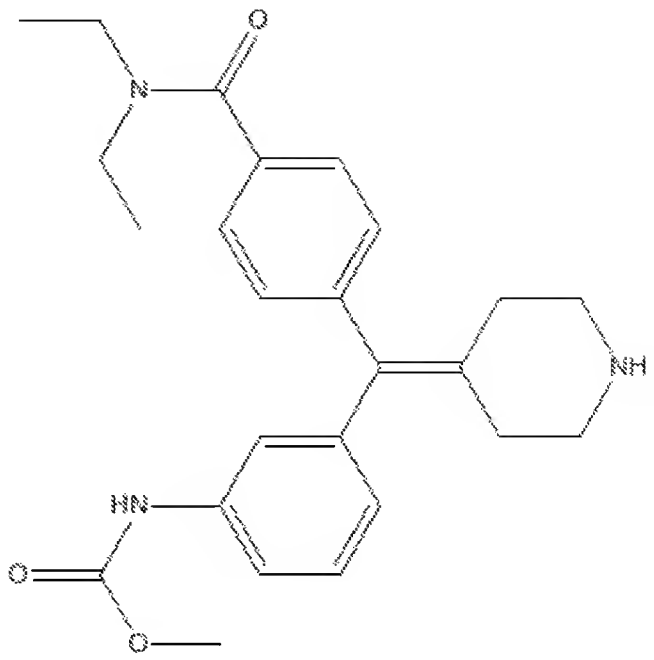
Greene teaches that nitrogen can be protected with various protecting groups such as benzyl optionally substituted with groups such as methoxy or hydroxy. See pages 531-539. It would have been obvious to one of ordinary skill in the art to produce a genus of compounds which overlap in subject matter with the '522 compounds and to deprotect the amino nitrogen in the piperidinyl ring so that amino nitrogen has a free hydrogen. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds and compositions over those of the generic prior art compounds and compositions.

Claims 1, 5, 8, 14 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 12 of copending Application No. copending Application No. 10541656 (US PG Pub 20060116399).

Although the conflicting claims are not identical, they are not patentably distinct from each other because because the copending application teaches a genus of compounds which overlap in subject matter with the instant genus of compounds and compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

'656 teaches the genus of compounds as shown in Formula III, where R4 is C1-6alkyl, and C3-6cycloalkyl, wherein said C-16alkyl and C3-6 cycloalkyl are optionally substituted with one or more groups selected from the moieties as claimed at lines 1-3, at page 6, and wherein R5 is hydrogen or C1-6 alkyl, R6 is hydrogen, and R2 and R3 are C2 alkyl. At pages 5-6, see the compound of formula III. The difference between the prior art compound and the instantly claimed compounds is the teaching of a generic compound which overlaps in subject matter with the instant genus of compounds. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. For

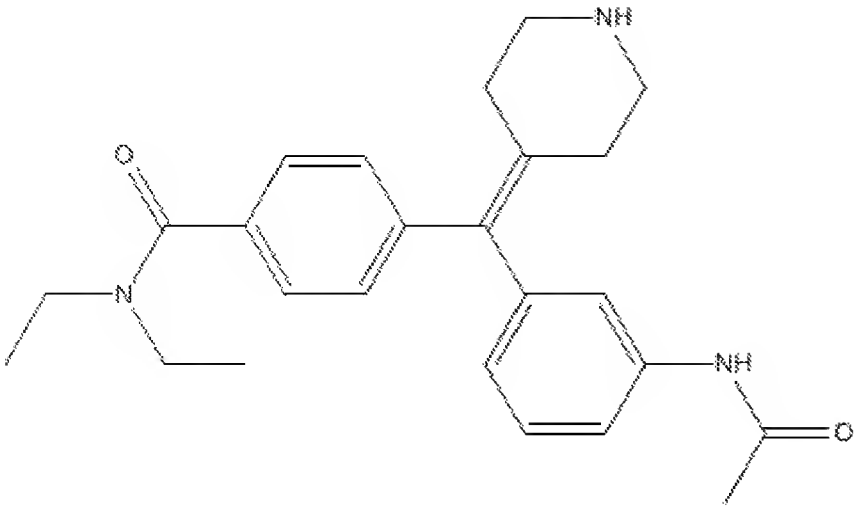
instance, see the compound,  of claim 22, where a disclosed species is exemplified. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

9. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

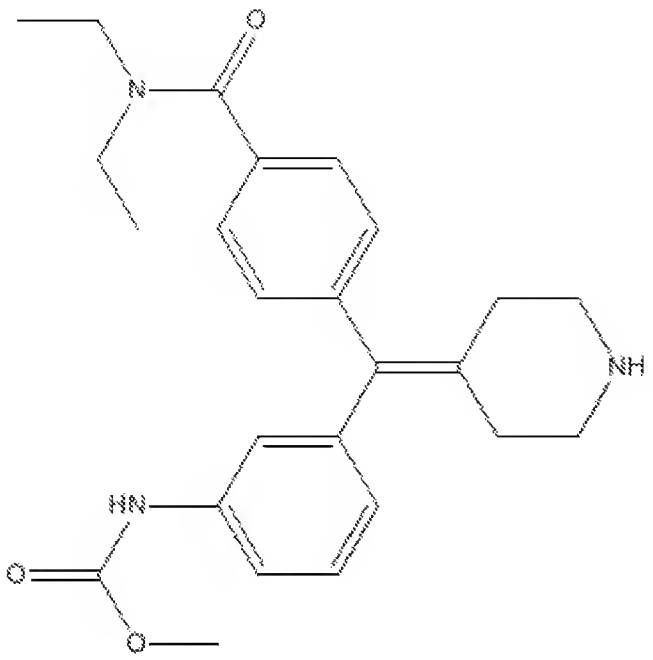
A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1, 5, 8 and 14 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 23 of copending Application No. 10541522, which

discloses the compound,




. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Claims 1, 5, 8 and 14 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 22 of copending Application No. copending Application No. 10541656 (US PG Pub 20060116399), which discloses the instant compound,



. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 14, 18-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the compounds of formula I with R1 equal to benzylaminocarbonyl, cyclopentyl, phenyl, cycloheptanyl, 2-chlorobenzoyl, 3-chlorobenzoyl, benzyl, 3-methylfuranyl, cyclohexyl, ethyl, 5-methylthien-2-yl)acetyl, 5-chlorothien-2-ylacetyl, 2-phenylpropanoyl, 2-phenylbutanoyl, benzoyl, anilinocarbonyl, piperidinecarbonyl, piperidinylmethylsulfonyl, phenylethyl, cyclohexylethyl,

dipropylcarbonyl, 1, 2, 3-benzotriazolecarbonyl; 1-methyl, 1,2, 3-benzotriazolecarbonyl, 3-pyridinecarbonyl, 2-methoxyphenylcarbonyl, 2-quinoxalinecarbonyl, 2,5-difluorophenylcarbonyl, 2-thiophenecarbonyl, methylphenylaminocarbonyl and wherein R1 and R2 come together to form a piperidine ring or pyrrolidine ring, R3 equal to hydrogen, and R2 equal to H, methyl, and ethyl, does not reasonably provide enablement for using the compounds of formula I where R1, R2,and R3 equal to any of the other moieties claimed. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized below:

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1)the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art 6) the amount of direction provided by the inventor 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

a) Determining if any particular claimed compounds with R1-R3 equal to any of the other moieties claimed other than those enabled above would be active would require synthesis of the substrate and subjecting it to testing with Applicants' GTP binding assay. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found in pages 39-75, which merely states Applicants' intent to make and use such compounds. c) In the instant case none of the working examples contains any radical R1-R3 equal to any of the moieties claimed other than the ones enabled above.

d)The state of the art is that is that the piperidinyl benzamide compound of cisapride has not been shown to have sustained positive effect in terms of therapeutic effectiveness in the treatment of gastroparesis. See PubMed Abstract: 1281070. Cisapride may only be considered a good alternative in cases where limited efficacy or side effects preclude the use of metoclopramide.

e) The nature of the invention is activity towards the delta opioid receptor and treatment of human diseases with Applicants' compounds. This involves physiological activity. The nature of the invention requires an

understanding of the receptor, the binding activity of small ligands to that receptor, and the ability of those compounds to modulate the delta opioid receptor. In view of the unpredictability of receptor binding activity and claimed divergent substituents with varied polarity, size, and polarisability, the skilled physician would indeed question the inclusion of such diverse rings, commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

f) There is no reasonable basis for the assumption that the myriad of compounds embraced by the present formula (I) will all share the same biological properties. For example, a cyclohexyl ring has different chemical properties than a thiophenyl ring. The diverse claimed compounds are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724 (compounds actually tested which demonstrated the asserted psychomotor stimulatory and anti-convulsant properties were those having the 3,4-dichlorophenyl substituent at the 2-position on the thiazolidone nucleus not sufficient for enablement of any heterocyclic radical at the same position).

*In re Fouche*, 169 USPQ 429 at 434 (a Markush group including both aliphatic and heterocyclic members not enabled for the use of those compounds within the claim having heterocyclic moieties.) *In re CAVALLITO AND GRAY*, 127 USPQ 202 (claims covering several hundred thousand possible compounds, of which only thirty are specifically identified in appellants' application, not enabled unless all of the thirty specific compounds disclosed had equal hypotensive potency because that fact would strongly indicate that the potency was derived solely from the basic structural formula common to all of them. A wide variation in such potency would suggest that it was due in part to the added substituents and might be eliminated or even reversed by many of the possible substituents which had not been tried.)

g) The artisan using Applicants' invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a heterocyclic ring would affect biological activity. In view of the divergent rings with varied basicity, steric hindrance, and polarisability, the skilled physician would indeed question the inclusion of such fused rings, commensurate in scope with these claims. g) Physiological activity, is well-

known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of millions of compounds of formula (I). Thus, the scope is very broad. The present claims embrace various heterocyclic radicals, which are not art-recognized as equivalent. The specific compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In the compound of formula V, the radical "Tf" is is unclear and indefinite because it is not defined at the claim.

**Response to applicant's remarks**

The obvious double patenting rejections over applications 10555980 and '850 are maintained, because they are not the only outstanding rejections in this office action.

Applicants traverse the rejection over Delorme (WO 98/28275), alleging that the present invention which comprises a substituted amino group in the meta position of the phenyl ring is a non-obvious difference over the unsubstituted amino group in Delorme in Example 41. The applicants allege that example 41 teaches away from the claimed invention. However, as noted in the 103 (a) rejection over Delorme above, example 41 is still nonobvious over the claimed invention, because it would have been obvious to one of ordinary skill in the art to protect a nitrogen with a nitrogen protecting group such as an acetyl group which is what the instant application discloses when R1 is R8C(O) and R8 is methyl. The compounds are structurally similar, but for the protection of the meta nitrogen group – which would motivate one of skill in the art to make the claimed compounds. Additionally, the Delorme compounds have very similar properties to the claimed genus of compounds. Like the claimed genus of compounds and compositions, the Delorme compounds are opioid agonists and are also analgesics. So because of

the similar properties and uses, one of ordinary skill in the art would also be motivated to modify the prior art compounds, to make the instant compounds and compositoins.

The applicant traverses the 112, first paragraph rejection made in the Final Office Action dated 1/4/08, asserting the research required to establish if the invention is enabled is routine. However, applicant offers no proof that the voluminous research is routine. Furthermore, R1 can be such nonobvious substituents such as C3-alkyl, or any C2-9heteroaryl-C1-4 alkyl ring and the compound of formula I . Applicant's specification does not provide sufficient guidance as to how the compounds of formula I's properties will change and be used as opioid agonists and analgesics when there are nonobvious changes in substituents such as R1 from C3-6 alkyl to C2-9 heteroaryl-C1-4alkyl. Furthermore, the state of the art indicates that piperidinylbenzamides such as Cisapride do not have sustained positive therapeutic effects on gastrointestinal disorders. See PubMed Abstract: 1281070.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

/Janet L. Andres/
Supervisory Patent Examiner, Art Unit 1625

BMR
July 8, 2008